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Urea Cycle, Properties and Applications of Urea

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Abstract: Urea, also known as carbamide, is an organic compound with chemical formula $\text{CO}(\text{NH}_2)_2$. This amide has two amino groups ($-\text{NH}_2$) joined by a carbonyl functional group ($-\text{C}(=\text{O})-$). It is thus the simplest amide of carbamic acid. Urea serves an important role in the metabolism of nitrogen-containing compounds by animals and is the main nitrogen-containing substance in the urine of mammals. Urea is New Latin, from French *urée*, from Ancient Greek *οὐρον* (*ouron*, “urine”), itself from Proto-Indo-European **h₂worsom*. It is a colorless, odorless solid, highly soluble in water, and practically non-toxic (LD50 is 15 g/kg for rats). [6] Dissolved in water, it is neither acidic nor alkaline. The body uses it in many processes, most notably nitrogen excretion. The liver forms it by combining two ammonia molecules (NH_3) with a carbon dioxide (CO_2) molecule in the urea cycle. Urea is widely used in fertilizers as a source of nitrogen (N) and is an important raw material for the chemical industry. In 1828 Friedrich Wöhler discovered that urea can be produced from inorganic starting materials, which was an important conceptual milestone in chemistry. This showed for the first time that a substance previously known only as a byproduct of life could be synthesized in the laboratory without biological starting materials, thereby contradicting the widely held doctrine of vitalism, which stated that only living organisms could produce the chemicals of life.³⁷

Keywords: urea, metabolism, non-toxic, excretion, fertilizers, chemicals of life, organic, amino groups, vitalism.

Introduction

In humans and mammals, almost 80% of the nitrogen excreted is in the form of urea, which is produced through a series of reactions occurring in the cytosol and mitochondrial matrix of liver cells.³⁸ These reactions are collectively called the urea cycle or the Krebs-Henseleit cycle. Ammonia is a toxic product of nitrogen metabolism which should be removed from our body. The urea cycle or ornithine cycle converts excess ammonia into urea in the mitochondria of liver cells. The urea forms, then enters the blood stream, is filtered by the kidneys and is ultimately excreted in the urine.¹

The overall reaction for urea formation from ammonia is as follows:



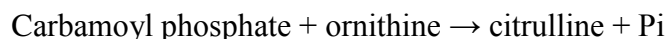
Steps in the Urea Cycle³⁶

The urea cycle is a series of five reactions catalyzed by several key enzymes. The first two steps in the cycle take place in the mitochondrial matrix and the rest of the steps take place in the cytosol. Thus the urea cycle spans two cellular compartments of the liver cell.²

- In the first step of the Krebs-Henseleit cycle, ammonia produced in the mitochondria is converted to carbamoyl phosphate by an enzyme called carbamoyl phosphate synthetase I. The reaction can be given as follows:³⁹

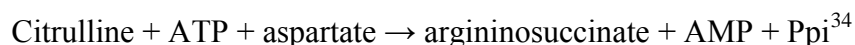


- The second step involves the transfer of a carbamoyl group from carbamoyl phosphate to ornithine to form citrulline. This step is catalyzed by the enzyme ornithine transcarbamoylase (OTC). The reaction is given as follows:³⁵

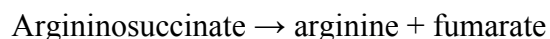


Citrulline thus formed is released into the cytosol for use in the rest of the steps of the cycle.³

- The third step is catalyzed by an enzyme called argininosuccinate synthetase, which uses citrulline and ATP to form a citrullyl-AMP intermediate, which reacts with an amino group from aspartate to produce argininosuccinate. This reaction can be given as follows:



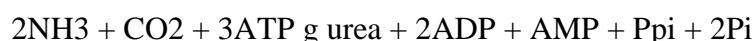
- The fourth step involves the cleavage of argininosuccinate to form fumarate and arginine. Argininosuccinate lyase is the enzyme catalyzing this reaction, which can be represented as follows:⁴⁰



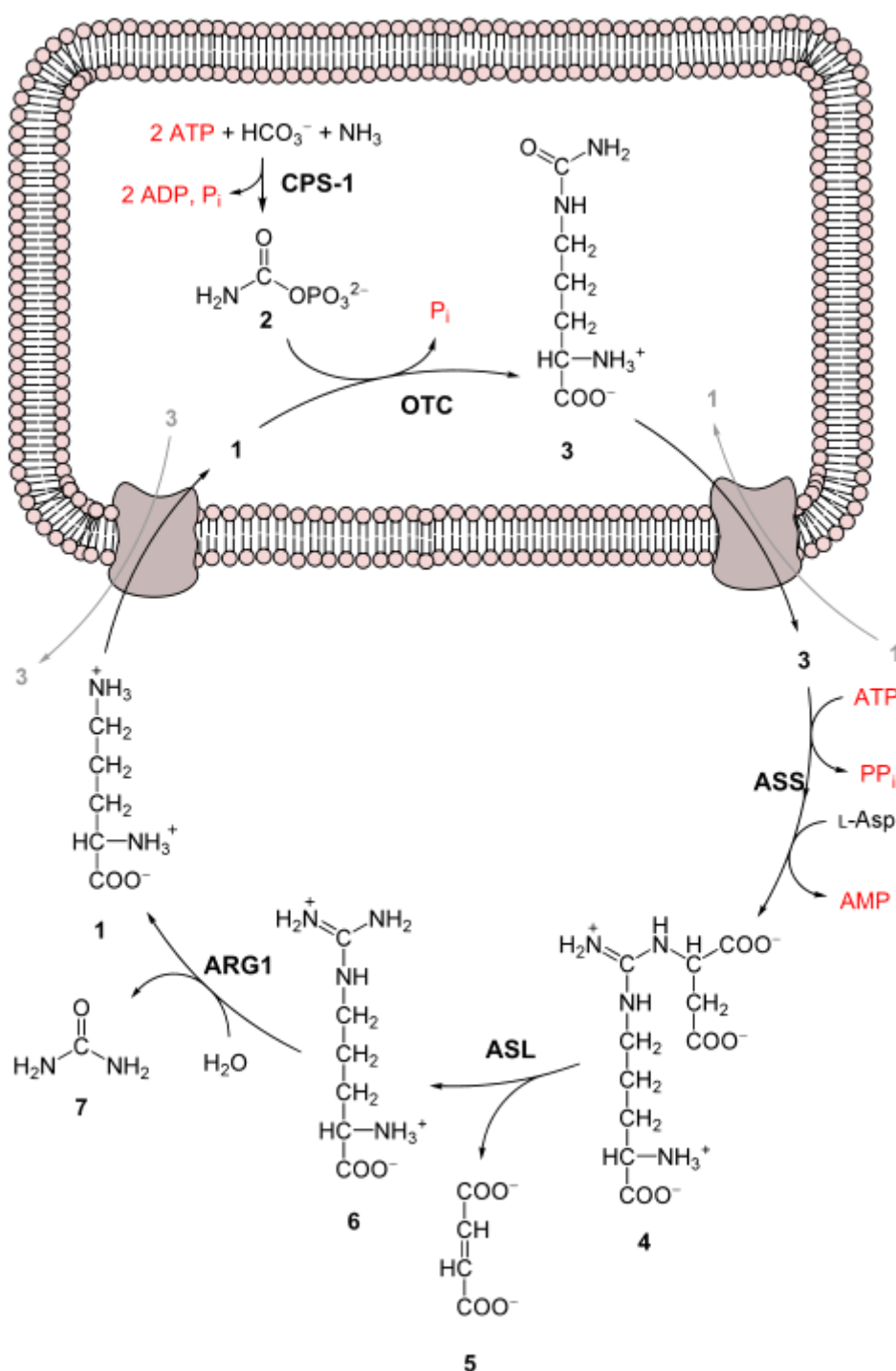
- In the fifth and last step of the urea cycle, arginine is hydrolyzed to form urea and ornithine. This is catalyzed by arginase and can be given as follows:³³



The overall reaction can be given as follows:⁴¹



Reactions of the urea cycle				
Step	Reactants	Products	Catalyzed by	Location
1	$\text{NH}_3 + \text{HCO}_3^- + 2\text{ATP}$	carbamoyl phosphate + $2\text{ADP} + \text{P}_i$	CPS1	mitochondria
2	carbamoyl phosphate + ornithine	citrulline + P_i	OTC, zinc, biotin	mitochondria
3	citrulline + aspartate + ATP	argininosuccinate + AMP + PP_i	ASS	Cytosol ³²
4	argininosuccinate	arginine + fumarate	ASL	cytosol
5	arginine + H_2O	ornithine + urea	ARG1, manganese	cytosol



Significance of the Urea Cycle

The main purpose of the urea cycle is to eliminate toxic ammonia from the body. About 10 to 20 g of ammonia is removed from the body of a healthy adult every day. A dysfunctional urea cycle would mean excess amount of ammonia in the body, which can lead to hyperammonemia and related diseases.³¹ The deficiency of one or more of the key enzymes catalyzing various reactions in the urea cycle can cause disorders related to the cycle. Defects in the urea cycle can cause vomiting, coma and convulsions in new

born babies. This is often misdiagnosed as septicemia and treated with antibiotics in vain. Even 1mm of excess ammonia can cause severe and irreversible damages.⁵

Diagnosis of Urea Cycle Defects

A blood aminogram is routinely used in the diagnosis of urea cycle disorders. The concentration of the nitrogen-carrying amino acids⁴², glutamine and alanine, in plasma is elevated in the case of OTC deficiency. In babies, elevated levels of orotic acid in the urine may be an indicator of OTC deficiency. Increased levels of blood citrulline and argininosuccinate are also seen in cases of citrullinemia.⁶

In older children, these disorders may present in the form of growth failure, psychomotor retardation and behavioral abnormalities³⁰. Hence, blood ammonia and urinary orotic acid monitoring and quantitation are crucial in patients with unexplained neurological symptoms.⁷

Discussion

Properties

Molecular and crystal structure⁴³

The urea molecule is planar. In solid urea, the oxygen center is engaged in two N–H–O hydrogen bonds. The resulting dense and energetically favourable hydrogen-bond network is probably established at the cost of efficient molecular packing: The structure is quite open, the ribbons forming tunnels with square cross-section.²⁹ The carbon in urea is described as sp^2 hybridized, the C–N bonds have significant double bond character, and the carbonyl oxygen is basic compared to, say, formaldehyde. Urea's high aqueous solubility reflects its ability to engage in extensive hydrogen bonding with water.⁸

By virtue of its tendency to form porous frameworks, urea has the ability to trap many organic compounds. In these so-called clathrates, the organic "guest" molecules are held in channels formed by interpenetrating helices composed of hydrogen-bonded urea molecules.^[7]

As the helices are interconnected, all helices in a crystal must have the same molecular handedness. This is determined when the crystal is nucleated and can thus be forced by seeding. The resulting crystals have been used to separate racemic mixtures.^[7]

Reactions

Urea is basic. As such it is protonated readily. It is also a Lewis base forming complexes of the type $[M(urea)_6]^{n+}$.²⁸

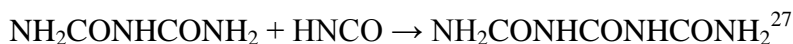
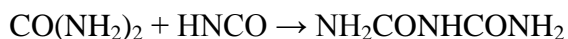
Urea reacts with malonic esters to make barbituric acids.⁹

Decomposition

Molten urea decomposes into ammonium cyanate at about 152 °C, and into ammonia and isocyanic acid above 160 °C:^[8]



Heating above 160 °C yields biuret $NH_2CONHCONH_2$ and triuret $NH_2CONHCONHCONH_2$ via reaction with isocyanic acid:^{[9][8]}



At higher temperatures it converts to a range of condensation products, including cyanuric acid $(CNOH)_3$, guanidine $HNC(NH_2)_2$, and melamine.^{[9][8]}

In aqueous solution, urea slowly equilibrates with ammonium cyanate.²⁶ This hydrolysis cogenerates isocyanic acid, which can carbamylate proteins, in particular the N-terminal amino group and the side chain amino of lysine, and to a lesser extent the side chains of arginine and cysteine.^{[10][11]} Each carbamylation event adds 43 daltons to the mass of the protein, which can be observed in protein mass spectrometry.^[11] For this reason, pure urea solutions should be freshly prepared and used, as aged solutions may develop a significant concentration of cyanate (20 mM in 8 M urea).^[11] Dissolving urea in ultrapure water followed by removing ions (i.e. cyanate) with a mixed-bed ion-exchange resin and storing that solution at 4 °C is a recommended preparation procedure.^[12] However, cyanate will build back up to significant levels within a few days.^[11] Alternatively, adding 25–50 mM ammonium chloride to a concentrated urea solution decreases formation of cyanate because of the common ion effect.^{[11][13]}

Analysis

Urea is readily quantified by a number of different methods, such as the diacetyl monoxime colorimetric method, and the Berthelot reaction (after initial conversion of urea to ammonia via urease)²⁵. These methods are amenable to high throughput instrumentation, such as automated flow injection analyzers^[14] and 96-well micro-plate spectrophotometers.^[15]

Ureas describes a class of chemical compounds that share the same functional group, a carbonyl group attached to two organic amine residues: $R^1R^2N-C(=O)-NR^3R^4$, where R^1 , R^2 , R^3 and R^4 groups are hydrogen (–H), organyl or other groups. Examples include carbamide peroxide, allantoin, and hydantoin. Ureas are closely related to biurets and related in structure to amides, carbamates, carbodiimides, and thiocarbamides.¹⁰

Results

Agriculture

More than 90% of world industrial production of urea is destined for use as a nitrogen-release fertilizer.^[9] Urea has the highest nitrogen content of all solid nitrogenous fertilizers in common use. Therefore, it has a low transportation cost per unit of nitrogen nutrient.²⁴ The most common impurity of synthetic urea is biuret, which impairs plant growth.⁴⁴ Urea breaks down in the soil to give ammonium ions (NH_4^+).²³ The ammonium is taken up by the plant through its roots. In some soils, the ammonium is oxidized by bacteria to give nitrate (NO_3^-), which is also a nitrogen-rich plant nutrient.⁴⁵ The loss of nitrogenous compounds to the atmosphere and runoff is wasteful and environmentally damaging so urea is sometimes modified to enhance the efficiency of its agricultural use. Techniques to make controlled-release fertilizers that slow the release of nitrogen include the encapsulation of urea in an inert sealant, and conversion of urea into derivatives such as urea-formaldehyde compounds, which degrade into ammonia at a pace matching plants' nutritional requirements.¹¹

Resins

Urea is a raw material for the manufacture of urea-formaldehyde resins, used mainly in wood-based panels such as particleboard, fiberboard and plywood.²²

Explosives

Urea can be used to make urea nitrate, a high explosive that is used industrially and as part of some improvised explosive devices.¹²

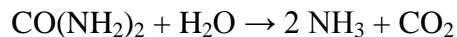
Automobile systems

Urea is used in Selective Non-Catalytic Reduction (SNCR) and Selective Catalytic Reduction (SCR) reactions to reduce the NO_x pollutants in exhaust gases from combustion from diesel, dual fuel,

and lean-burn natural gas engines. The BlueTec system, for example, injects a water-based urea solution into the exhaust system. Ammonia (NH_3) first produced by the hydrolysis of urea reacts with nitrogen oxides (NO_x) and is converted into nitrogen gas (N_2) and water within the catalytic converter. The conversion of noxious NO_x to innocuous N_2 is described by the following simplified global equation:^[16]



When urea is used, a pre-reaction (hydrolysis) occurs to first convert it to ammonia:



Being a solid highly soluble in water (545 g/L at 25 °C),^[2] urea is much easier and safer to handle and store than the more irritant, caustic and hazardous ammonia (NH_3), so it is the reactant of choice. Trucks and cars using these catalytic converters need to carry a supply of diesel exhaust fluid, also sold as AdBlue, a solution of urea in water.^[13]

Laboratory uses

Urea in concentrations up to 10 M is a powerful protein denaturant as it disrupts the noncovalent bonds in the proteins.^[21] This property can be exploited to increase the solubility of some proteins. A mixture of urea and choline chloride is used as a deep eutectic solvent (DES), a substance similar to ionic liquid. When used in a deep eutectic solvent, urea gradually denatures the proteins that are solubilized.^[17]

Urea can in principle serve as a hydrogen source for subsequent power generation in fuel cells. Urea present in urine/wastewater can be used directly (though bacteria normally quickly degrade urea). Producing hydrogen by electrolysis of urea solution occurs at a lower voltage (0.37 V) and thus consumes less energy than the electrolysis of water (1.2 V).^[18]

Urea in concentrations up to 8 M can be used to make fixed brain tissue transparent to visible light while still preserving fluorescent signals from labeled cells. This allows for much deeper imaging of neuronal processes than previously obtainable using conventional one photon or two photon confocal microscopes.^[19]

Medical use

Urea-containing creams are used as topical dermatological products to promote rehydration of the skin. Urea 40% is indicated for psoriasis, xerosis, onychomycosis,^[20] ichthyosis, eczema, keratosis, keratoderma, corns, and calluses. If covered by an occlusive dressing, 40% urea preparations may also be used for nonsurgical debridement of nails. Urea 40% "dissolves the intercellular matrix"^{[20][21]} of the nail plate. Only diseased or dystrophic nails are removed, as there is no effect on healthy portions of the nail.^[22] This drug (as carbamide peroxide) is also used as an earwax removal aid.^[23]

Urea has also been studied as a diuretic. It was first used by Dr. W. Friedrich in 1892.^[24] In a 2010 study of ICU patients, urea was used to treat euvoletic hyponatremia and was found safe, inexpensive, and simple.^[25]

Like saline, urea has been injected into the uterus to induce abortion, although this method is no longer in widespread use.^[26]

The blood urea nitrogen (BUN) test is a measure of the amount of nitrogen in the blood that comes from urea. It is used as a marker of renal function, though it is inferior to other markers such as creatinine because blood urea levels are influenced by other factors such as diet, dehydration,^[27] and liver function.^[19]

Urea has also been studied as an excipient in Drug-coated Balloon (DCB) coating formulation to enhance local drug delivery to stenotic blood vessels.^{[28][29]} Urea, when used as an excipient in small doses ($\sim 3 \mu\text{g}/\text{mm}^2$) to coat DCB surface was found to form crystals that increase drug transfer without adverse toxic effects on vascular endothelial cells.^[30]

Urea labeled with carbon-14 or carbon-13 is used in the urea breath test, which is used to detect the presence of the bacterium *Helicobacter pylori* (*H. pylori*) in the stomach and duodenum of humans, associated with peptic ulcers. The test detects the characteristic enzyme urease, produced by *H. pylori*, by a reaction that produces ammonia from urea. This increases the pH (reduces the acidity) of the stomach environment around the bacteria. Similar bacteria species to *H. pylori* can be identified by the same test in animals such as apes, dogs, and cats (including big cats).¹⁴

Miscellaneous uses

- An ingredient in diesel exhaust fluid (DEF), which is 32.5% urea and 67.5% de-ionized water. DEF is sprayed into the exhaust stream of diesel vehicles to break down dangerous NO_x emissions into harmless nitrogen and water.¹⁸
- A component of animal feed, providing a relatively cheap source of nitrogen to promote growth
- A non-corroding alternative to rock salt for road de-icing.^[31] It is often the main ingredient of pet friendly salt substitutes although it is less effective than traditional rock salt or calcium chloride.^[32]
- A main ingredient in hair removers such as Nair and Veet¹⁵
- A browning agent in factory-produced pretzels
- An ingredient in some skin cream,^[33] moisturizers, hair conditioners, and shampoos
- A cloud seeding agent, along with other salts^[34]
- A flame-proofing agent, commonly used in dry chemical fire extinguisher charges such as the urea-potassium bicarbonate mixture
- An ingredient in many tooth whitening products
- An ingredient in dish soap¹⁶
- Along with diammonium phosphate, as a yeast nutrient, for fermentation of sugars into ethanol
- A nutrient used by plankton in ocean nourishment experiments for geoengineering purposes
- As an additive to extend the working temperature and open time of hide glue
- As a solubility-enhancing and moisture-retaining additive to dye baths for textile dyeing or printing^[35]
- As an optical parametric oscillator in nonlinear optics^{[36][37]}

Conclusions

Urea can be irritating to skin, eyes, and the respiratory tract. Repeated or prolonged contact with urea in fertilizer form on the skin may cause dermatitis.^[44] High concentrations in the blood can be damaging.⁴⁶ Ingestion of low concentrations of urea, such as are found in typical human urine, are not dangerous with additional water ingestion within a reasonable time-frame. Many animals (e.g. camels, rodents or dogs) have a much more concentrated urine which may contain a higher urea amount than normal human urine¹⁷. Urea can cause algal blooms to produce toxins, and its presence in the runoff from fertilized land may play a role in the increase of toxic blooms.^[45] The substance decomposes on heating above melting

point, producing toxic gases, and reacts violently with strong oxidants, nitrites, inorganic chlorides, chlorites and perchlorates, causing fire and explosion.^[46]

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